Table 2. Characteristics of the Hydrotherapy Sessions and Water Quality

Duration per session, mean (range), min	29.6 (15–40)
Type of exercises*	
Movements in supine position	72%
Swimming (back stroke)	12%
Seated position	36%
Standing position	64%
Walking	56%
Rate of complications (95% confidence interval)	0% (0–4.1%)
Number of sessions during intensive care unit stay	
Total	88
Median (interquartile range)	2 (1–3)
Mean (range)	3.5 (1–20)
Microbiological screening of pool water (17 samples in 15 mo)	
Coagulase-negative *Staphylococcus*	2 (1 and 2 cfu)
Gram-negative rods, not *Pseudomonas*	2 (43 and 27 cfu)
Nonfermative gram-negative rods	3 (51, 22, and 55 cfu)

*Exercises could be combined during one session.

that hydrotherapy was performed in a university hospital with extensive experience with early mobilization in ICU patients. No patient reported discomfort or exhibited severe oxygen desaturation or hemodynamic instability. No interventions were needed to improve hemodynamics.

In addition to immediate complications, transmission of infections through contaminated water was an initial concern. However, microbiological screening of pool water did not reveal any relevant contamination.

In conclusion, hydrotherapy appears to be a feasible and safe intervention in selected critically ill ventilated patients. Future studies are needed to evaluate potential clinical benefits and cost-effectiveness. ■

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Karin M. Felten-Barentsz, P.T., M.Sc.
Antonius J. C. Haans, R.T.
Radboud University Medical Centre
Nijmegen, The Netherlands

Arthur S. Slutsky, M.D.
St. Michael's Hospital
Toronto, Ontario, Canada
and
University of Toronto
Toronto, Ontario, Canada

Leo M. A. Heunks, M.D., Ph.D.
Johannes G. van der Hoeven, M.D., Ph.D.
Radboud University Medical Centre
Nijmegen, The Netherlands

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Early Peripheral Perfusion–guided Fluid Therapy in Patients with Septic Shock

To the Editor:

Septic shock remains the most frequent cause of death in patients admitted to the intensive care unit (ICU) (1). Careful titration of therapy is essential; undertreatment results in persistence of impaired tissue oxygenation, whereas overtreatment leads to a positive fluid balance that can result in pulmonary edema, prolonged mechanical ventilation, and finally death (2–6). Although peripheral perfusion alterations are stronger predictors of outcome than systemic hemodynamic variables in patients with septic shock, end points to guide volume resuscitation are still based on systemic parameters, and little is known about resuscitation guided by endpoints of peripheral tissue perfusion (7–9). We therefore undertook a proof-of-concept randomized controlled study comparing early goal-directed fluid resuscitation based on clinical assessment of peripheral perfusion with standard fluid therapy to investigate whether peripheral perfusion–guided resuscitation is feasible and would lead to less fluid administration in patients with septic shock. Some of the results of these studies have been previously reported in the form of an abstract (10).

Clinical trial registered with www.clinicaltrials.gov (NCT 01397474).

Author Contributions: M.E.v.G. conducted the study, analyzed and interpreted the data, and drafted the manuscript. N.E. assisted in conducting the study. R.J.P.v.d.V. assisted in analyzing the data and reviewed the final data. A.L. assisted in the design of the study and assisted in conducting the study and participated in data interpretation and statistical analysis. E.K. assisted in the design of the study and data interpretation. J.B. assisted with study design and manuscript preparation. J.v.B. conceived the study, participated in its design and coordination, and reviewed the manuscript. All authors read and approved the final manuscript.

This letter has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Methods

This trial was approved by the Erasmus MC Institutional Review Board. Deferred proxy consent was obtained from a relative authorized to consent on behalf of each patient.

In brief, we performed a prospective randomized controlled pilot study in patients with septic shock admitted to the ICU; more details are listed in the online supplement. Directly after ICU admission, patients were randomly assigned into the control group or the intervention group (peripheral perfusion–targeted fluid management [PPTFM] group) to determine the resuscitation strategy during the first 6 hours. In the PPTFM group, fluid management was based on peripheral tissue

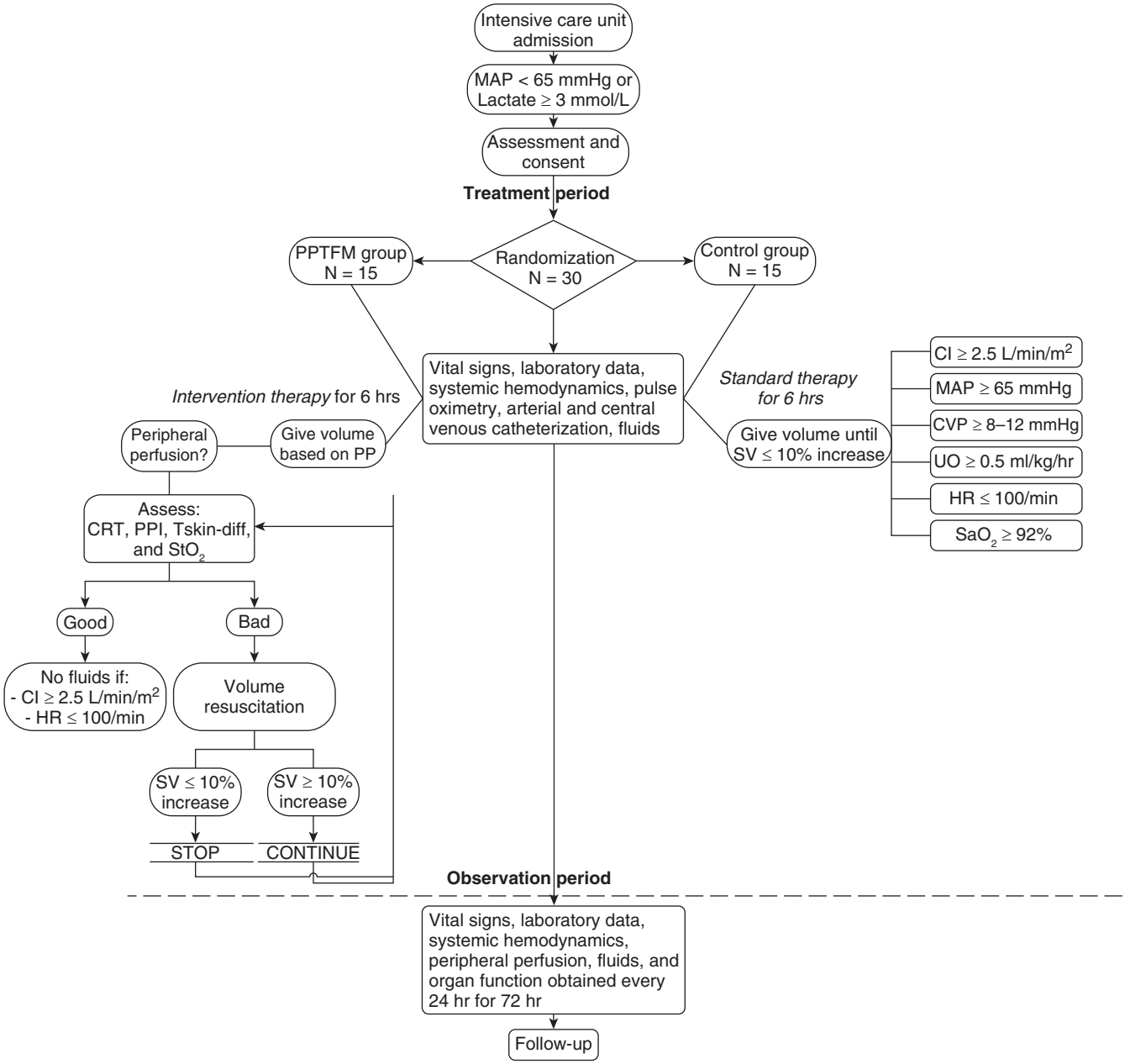

Figure 1. Study algorithm for the first 6 hours of intensive care unit admission (control vs. peripheral perfusion–targeted fluid management [PPTFM] group). In the control group, fluid resuscitation was based on systemic hemodynamic parameters. In the intervention group, treatment was based on peripheral perfusion parameters: if three of four parameters were considered impaired, a fluid challenge (250 ml colloids in 15 minutes) was administered, aiming at an increase in peripheral perfusion. If peripheral perfusion parameters did not improve after two consecutive challenges, fluid administration was stopped. CI = cardiac index; CRT = capillary refill time; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; PP = peripheral perfusion; PPI = peripheral perfusion index; Sa_{O_2} = arterial exygenation; St_{O_2} = tissue oxygenation saturation; SV = stroke volume; Tskin-diff = forearm-to-fingertip skin temperature gradient; UO = urine output.

perfusion parameters: the capillary refill time, the peripheral perfusion index, the forearm-to-fingertip body temperature gradient, and the tissue oxygenation saturation (11). Only patients with "poor peripheral perfusion" (i.e., three of four parameters altered) were considered suitable for fluid repletion (Figure 1). In the control group, hemodynamic goals were based on the 2012 Surviving Sepsis guidelines (12). We assessed protocol adherence at 2, 4, and 6 hours after study entry. Thereafter, data were collected daily until 72 hours after study entry (observation period). More details are provided in the online supplement.

We used linear mixed-model analyses to calculate differences between groups in systemic hemodynamics, peripheral perfusion parameters, laboratory variables, and fluid therapy over time (*see* the online supplement).

Results

Thirty patients were included, of whom 15 were allocated to each group. Baseline characteristics of all patients are shown in Table E1 in the online supplement. Both groups were well matched, and there were no statistical differences between groups at baseline. During the study period, we observed no significant difference between groups in systemic hemodynamic parameters and peripheral perfusion parameters. Importantly, the two groups had similar lactate concentrations and central venous oxygen saturation values over time. PPTFM patients received less mean (standard error) fluids during the treatment period (4,227 [1,081 ml] vs. 6,069 [1,715 ml]; $P = 0.39$), and almost 2.5 L less during the observation period (7,565 [982 m] vs. 10,028 [941 ml]; $P = 0.08$) in the control group (Table 1). Interestingly, patients in the control group stayed longer in the hospital compared with PPTFM patients, with 43 (8) versus 16 (3) days ($P = 0.05$), and had a higher organ failure scores (Sequential Organ Failure Assessment total scores and neurologic subscores).

Table 1. Fluid Therapy and Outcome Variables

Variables and Groups	Study Period	
	0–6 h	7–72 h
Cumulative fluids, ml		
Control	6,069 (1,715)	10,028 (941)
PPTFM	4,227 (1,081)	7,565 (982)
Urine output, ml		
Control	520 (160)	2,469 (542)
PPTFM	332 (84)	1,680 (527)
$SOFA_{total}$		
Control	12.8 (10.0–16.8)	11.0 (5.3–15.3)
PPTFM	11.5* (8.0–13.0)	8.3 (5.5–13.1)
Mechanical ventilation free days, d		
Control	2 (2–6)	
PPTFM	2 (1–5)	
Intensive care unit mortality, n (%)		
Control	6 (40)	
PPTFM	7 (47)	
Intensive care unit stay, d		
Control	8 (3–8)	
PPTFM	10 (2–10)	
Hospital stay, d		
Control	43 (8–45)	
PPTFM	16 (5– 28)*	

Definition of abbreviations: PPTFM = peripheral perfusion–targeted fluid management; SOFA = Sequential Organ Failure Assessment.
Data are presented as mean (SE) or mean (interquartile range) unless otherwise stated. Dash (–) indicates the mean value between subsequent points during the study periods for the period from 0 to 6 hours and for the period from 7 to 72 hours.
*$P < 0.05$ between groups (control vs. PPTFM).

Discussion

This proof-of-concept study shows that early peripheral perfusion–targeted fluid resuscitation leads to a trend toward less fluids when compared with a conventional regimen, based on systemic hemodynamic parameters.

Although the difference in fluid administration was not significant, PPTFM patients received almost 2 L less in just the first 6 hours, leading up to 2.5 L less 72 hours after ICU admission. If performed on a larger scale, this could have important clinical implications, as large volumes of fluids are associated with pulmonary and renal failure and adverse outcomes (13). One can hypothesize that, using our algorithm for targeting the peripheral circulation, less fluids are administered because infusion is stopped earlier: as soon as peripheral perfusion is not impaired (anymore) or when perfusion remains impaired, although maximum cardiac output is reached. Surprisingly, we observed that PPTFM patients have a significantly shorter hospital length of stay and significantly lower organ failure scores. It must, however, be noted that our study was not powered for this purpose, so these results should be interpreted with caution. A larger trial is needed to confirm and elaborate our findings.

Still, to our knowledge, this is the first randomized controlled study that incorporates peripheral perfusion parameters as a target for fluid resuscitation in patients with septic shock. In our opinion, this approach provides an important complement to currently targeted systemic hemodynamic parameters. From a physiological point of view, peripheral tissues are the first to reflect hypoperfusion during shock and are the last to reperfuse during resuscitation, as a result of compensatory sympathetic nervous system activation (14). If this response is adequate, restored peripheral perfusion indicates that enough fluid has been administered and a conservative strategy can be followed. It therefore makes sense to strive toward a more tissue perfusion–based approach that allows the physician to titrate therapy in a way conventional targets such as blood pressure and urine production do not provide. These considerations, as well as the limitations of our study, are elaborated in the online supplement.

Further research is needed to confirm our findings and definitely demonstrate whether the use of peripheral perfusion parameters as resuscitation targets can benefit outcome in critically ill patients. ■

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Michel E. van Genderen, M.Sc.
Noel Engels, M.Sc.
Ralf J. P. van der Valk, M.D., Ph.D.
Alexandre Lima, M.D., Ph.D.
Eva Klijn, M.D.
Jan Bakker, M.D., Ph.D.
Jasper van Bommel, M.D., Ph.D.
Erasmus MC
Rotterdam, The Netherlands

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Relation between Recurrence of Tuberculosis and Transitional Changes in IFN-γ Release Assays

To the Editor:

Although IFN-γ release assays (IGRAs) have been reported to be useful as monitoring tools during and after treatment (1–4), a relationship between IGRAs and recurrence of tuberculosis (TB) has not been studied. We evaluated the transitional changes in IFN-γ response by the QuantiFERON-TB Gold test (QFT-G; Cellestis, Carnegie, Victoria, Australia) in patients with TB from before treatment to 2 years after completion of treatment and studied a relationship between recurrence of TB and the changes in IFN-γ response. Some of the results of these studies have been previously reported in the form of an abstract (5).

Between April 2007 and April 2009, 49 Japanese patients with active TB were enrolled in a prospective cohort study at the Jikei University Daisan Hospital. All patients received treatment according to the guidelines of the Treatment Committee of the Japanese Society for Tuberculosis (6) by directly observed treatment. QFT-G was performed in all patients before the beginning of treatment (baseline [BL]) and was repeated at the completion of treatment (time 0 [T0]) and at 3, 6, 9, 12, 18, and 24 months after completion of treatment (T3, T6, T9, T12, T18, and T24, respectively). The results were evaluated according to the Centers for Disease Control and Prevention guidelines (7). The ethical committee at the Jikei University approved this study, and written informed consent was obtained from all patients. The transitional changes in IFN-γ response to early secreted antigenic target (ESAT)-6 and culture filtrate protein (CFP)-10 were calculated by subtracting BL from the observed response at other points. Chi-square and Fisher's exact tests were used to compare paired proportions. The Mann-Whitney U test was used to compare differences of average values. A P value < 0.05 indicated statistical significance for all analyses.

The clinical characteristics and treatment regimen of the 49 patients with and without recurrence are shown in Table 1. We successfully obtained the results of culture conversion from sputum in all patients, and all patients successfully completed treatment with recovery from symptoms and significant improvement of their chest radiograph findings. Unfortunately, three patients had recurrence at 3, 4, and 7 months after completion of treatment (patients 1, 2, and 3, respectively) and underwent retreatment. None of the other patients had recurrence for 2 years after

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